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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/801,933	03/07/2001	Brett C. Bookser	030727.0042.CIP1	3455

7590 11/25/2002

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EXAMINER	
MCKENZIE, THOMAS C	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 11/25/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/801,933	BOOKSER ET AL.	
	Examiner	Art Unit	
	Thomas McKenzie Ph.D.	1624	

-- The MAILING DATE f this communication appears n the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 August 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) *7* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 8-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 8-7 ar
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to amendments filed on 8/19/02. Applicants have amended claims 1, 14, and 30. There are thirty-six claims pending and thirty-five under consideration. Claims 1-6 and 8-33 are compound claims. Claims 34-36 are use claims. This is the second action on the merits. The application concerns some phenyl phosphonate compounds and uses thereof. Applicants' efforts in supplying a copy of all presently pending claims in amended form is greatly appreciated. Applicants' two amendments to the specification correct minor typos and do not introduce any new matter.

Election/Restrictions

2. This application contains claim 7 drawn to an invention nonelected with traverse in Paper No. 9. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

3. Objection is made to claims s 1-6, 8-29, and 31-36 as containing non-elected subject matter. The claimed compounds, compositions, and methods that employ them present a variable core. Formula I(b) contains compounds drawn to the non-elected inventions with X other than carbon. Formula I(a) is drawn to non-elected inventions.

4. Applicants' remarks concerning linking claims are noted. No linking claims have been allowed and the linking claims contain subject matter that has not been searched. PTO policy has changed concerning rejecting non-elected subject matter but Applicants are urged to amend their claims so that it need not be done after allowance.

Information Disclosure Statement

5. Applicants IDS (PTO-1449), entered as paper #8 and filed 1/29/02 is noted. However, none of the cited references is presently with the file and the search initiated during the first office action was not productive. A second search has been requested but prudence suggests that Applicants provide a second copy of the documents.

Response to Arguments

6. Applicants correctly pointed out that radical R^2 consists of R^3 and hydrogen. The variable OR^2, which is a possible constituent of J^2-J^6 thus, consists of OR^3 and OH. Applicants' OR^3 limitation in claim 30 for J^2-J^6 , although not so claimed *in haec verba* in claim 1, is a narrowing of the OR^2 definition of claim 1. Thus, the indefiniteness rejection made in point #9 is withdrawn. Applicants' citation of Stedman's definition of glycogenosis as seven specific types (Cori classification) of a recessive inherited disease and the equivalence of these diseases with

"glycogen storage diseases". Is persuasive. Thus, the indefiniteness rejection made in point #11 is withdrawn.

Claim Rejections - 35 USC § 112

7. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Claims 1-6, 8-17, 19, 26, 30, and 34-36 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase in line 16, page 144 "optionally substituted alicyclic where the cyclic moiety contains a carbonate or thiocarbonate" is indefinite. While applicant may be his or her own lexicographer, a term in a claim may not be given a meaning repugnant to the usual meaning of that term. See *In re Hill*, 161 F.2d 367, 73 USPQ 482 (CCPA 1947). The term "alicyclic" in claim 1 is used by the claim to mean "alicyclic or saturated heterocyclic," while the accepted meaning is "any aliphatic compound that contains a ring of carbon atoms", BioTech's Life Science Dictionary, copyright 1995-98. The Condensed Chemical Dictionary defines the term as "... carbon atoms in closed ring structures". An alicyclic ring may contain multiple bonds but may not be aromatic and may not contain any heteroatoms.

Applicants have clarified that they intend the carbonate or thiocarbonate functional groups to be within the ring not substituents upon the ring. It makes no

difference how Applicants' define alicyclic in the specification. That definition is repugnant to the art-recognized use of the term alicyclic. The Examiner suggests removing the reference to containing such non-carbon atoms.

8. Claims 1-6 and 8-36 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "pharmaceutically acceptable prodrugs ... thereof" occurs near the end of claim 1. The phrase "prodrugs thereof" is indefinite. The issue on second paragraph is whether the structures of the claimed compounds are clearly defined. Applicants' prodrugs are molecules whose structure lie outside the subject matter of formula I, but upon metabolism in the body are converted to active compounds falling within the structural scope of formula I. The claim describes the function intended but provides no specific structural guidance to what constitutes a "prodrug". Structural formulas, names, or both can accurately describe organic compounds, which are the subject matter of claim 1. Attempting to define means by function is not proper when the means can be clearly expressed in terms that are more precise.

Applicants correctly point out that their prodrugs are within the scope of claim 1. The Examiner better expresses the concept by noting that their prodrugs are not within the scope of the structural formula given in the claim 1. Applicants

point to the amended paragraph spanning pages 10 to 11 to clarify the structures they intend. This is not persuasive for four reasons. Firstly, the passage provides limited structural guidance and defines the phrase in terms of itself. We know what the concept of prodrug entails. What we do not know is what specific compounds Applicants claim. Secondly, the passage uses open language "includes but is not limited to". "The groups illustrated are exemplary, not exhaustive". Thirdly, prodrugs of hydroxyl, thiol, and amine containing drugs include 'acyl" esters. Presumably, amine ester means amides since carbamate derivates of amines are covered by "alkoxycarbonyl". The enablement question for amides is considered separately below. The accepted meaning of the term "acyl" is "any acid substituent with the OH group removed". Does this include the acids of boron and nitrogen? What is the specific stem, i.e. if acyl is RC(O), what is R? Is it limited to alkanoic acids? Are aromatic, heteroaromatic, alkyl radicals substituted by anything permitted? Are there any limitations?

Applicants point to Examples 17 and 18 and assert that the term prodrug is well established in the art. This is also not persuasive. Example 17 is drawn to the synthesis of compounds of formula (I) where both $R^1Y = NHCHR^{13}CO_2R^{14}$. The Examiner is interpreting "amino acid ester" in line 3 and line 6, page 131 to mean an alkyl ester of a naturally occurring α-amino acid. Example 18 is drawn to

compounds of formula (I) where only one of $R^1Y = NHCHR^{13}CO_2R^{14}$. The Examiner has no opinion whether these compounds are, in fact, prodrugs. However, both compounds fall within the scope of formula (I) and fail to clarify which compounds lying outside the scope of formula (I) are intended. Secondly, assertion is not evidence. In the discussion of enablement of prodrug, the Examiner cites references showing the lack of recognition in the art of medicinal chemistry of what structurally constitutes a prodrug. The Examiner suggest using the language from the passage spanning line 11, page 11 to line 26, page 15. to indicate which prodrugs they intend.

9. Claim 34 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "a fructose-1,6-bisphosphatase dependent disease" is indefinite. The claim provides for the use of the compounds of formula I, but the claims do not set forth any steps involved in determining how to identify "a fructose-1,6-bisphosphatase dependent disease". It is unclear what diseases and treatments applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how to practice this use. Identifying which diseases applicants intend this claim to cover will involve extensive and potentially inconclusive clinical

research. With out such clinical research to identify the patients and diseases applicants intend to treat, one skilled in the art cannot determine the metes and bounds of the claim. Hence, the claim is indefinite.

Applicants cite Stedman's definition of fructose bisphosphatase and descriptions of the condition fructose-1,6-diphosphatase deficiency from two medical textbooks Harrison's and Schiff's in support of their assertion that the phase is art-recognized in clinical medicine. This is not persuasive for two reasons. Firstly, deficiency and dependency are hardly the same thing. In fact, they have opposing meanings. Secondly, the three references make clear that the fructose-1,6-diphosphatase deficiency is an autosomal recessive disorder leading to hypoglycemia and lactic acidosis, Harrison's, page 2209. Applicants however, state in lines 9-10, page 113 that compound which inhibit the enzyme fructose-1,6-diphosphatase, such as their claimed compounds, may be used to "treat diabetes mellitus, lower blood glucose levels, and inhibit gluconegensis." Diabetes is characterized by hyperglycemia. Would not a physician treat "a fructose-1,6-bisphosphatase dependent disease" with an enzyme inhibitor? Inhibiting the enzyme, which Applicants' compounds do, would not seem like a logical way to treat a lack of the enzyme.

Since glucose levels are not a disease, the Examiner suggests claiming treatment of diabetes mellitus, and gluconegensis, relying upon lines 9-10, page 113 for support.

10. Claims 1-6 and 8-36 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Determining if a particular substance is a "prodrug" will involve undue experimentation. For a compound to be a prodrug, it must meet three tests. It must itself be biologically inactive. It must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be biologically active. Determining whether a particular compound meets these three criteria in a clinical trial setting passes the threshold of undue experimentation.

Applicants make four arguments concerning enablement for prodrugs. Firstly, they assert that the experimentation described above is routine. Secondly, the state that aspirin and hexamine, developed in the nineteenth century are prodrugs. Thirdly, they cite five publications alleging that synthesis of prodrugs is routine. Fourthly, they point to Examples 17 and 18, discussed above, and point

out that one working example, when correlated to the scope of the claims, is sufficient for enablement.

The factors to be considered in an enablement rejection have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, and the predictability or unpredictability of the art. *Ex parte Formal*, et al., 230 USPQ 546.

Wolff (Burger's Medicinal Chemistry) in section 9.1 states prodrug development requires collaboration between the skilled medicinal chemists and metabolism specialists. All would have a Ph. D. degree and several years of industrial experience. Wolff (Burger's Medicinal Chemistry) in section 9.1 outlines the research program that must be undertaken to prepare a prodrug. In that paragraph, the difficulties of extrapolating between species in prodrug development are discussed. Thus, the question as to whether a compound is a prodrug in humans will require clinical studies. The guidance concerning the prodrugs in the specification is found in formulas VI-VIII in pages 30-31, in the synthesis passage beginning at line 20, page 100, and more specifically in the passage spanning line 11, page 11 to line 26, page 15. The working examples to

which Applicants point are Examples 17 and 18. The invention concerns chemical synthesis and the pharmacokinetic properties of drug molecules. The state of the art is provided by the references cited by Applicants and the Examiner. The skill and predictability in the art are discussed below.

Applicants use the word prodrug in two different ways. They assert that compounds of formula I are themselves prodrugs and Applicants claim additional compounds that produce formula (I) upon metabolism. The Examiner has no view whether all, most, some, or any of the compounds of formula (I) are prodrugs. The issue is the compounds whose structures are not defined but lie outside the scope of formula (I). Formulas VI-VIII are embraced by formula (I) and do not provide guidance to the structures of those out that scope. The passage beginning at line 20, page 100 is labeled synthesis of prodrugs but in fact, outlines synthesis of formula (I) and does not provide any guidance to the structures of those out that scope. There are nine types of prodrugs disclosed in the passage spanning line 11, page 11 to line 26, page 15. Most are covered by formula (I) but Formula B, page 11, the right side of Formula E, page 13, Formulas E1, E-2, E3-, and F, page 14, the trichloroethyl ester in the last paragraph on page 15 are outside the scope of formula (I) and constitute guidance in the specification.

Examples 17 and 18, page 130-131, lack any chemical data characterizing the products, and fail to specify the staring materials used, stating only an "aminoacid ester" is to be used. The two examples give no biological data and do not offer any evidence whether the products of these reactions are or are not prodrugs. Thus, these are prophetic, not working examples. In addition, as discussed above, these do not bear on the question of compounds lying outside the scope of formula (I). In Example I, spanning pages 138-139, Applicants describe a protocol for determining if a compound is a prodrug in rats. There are no results reported and it is unclear if any of the compounds lying outside the scope of formula (I) have been tested in this protocol. Thus, Applicants have provided no working examples of a prodrug.

Sanchez (J. Med. Chem.) in the four sentences spanning page 1766 implies that the prodrug nature of an alanate ester was only found empirically after the compound was made. Serafinowska (J. Med. Chem.) in the last complete paragraph on the left side of page 1375 describes the synthesis of thirty-eight potential prodrug phosphonate esters and two amides. Nineteen of these displayed the measurable bioavailability. Of these, only seven had bioavailability greater than 10% required of a successful prodrug. It appears that only three of these

substances were further evaluated as possible prodrugs. Thus, the skill in the art of synthesis of prodrugs would appear low and not predictable as of 1995.

Bundgaard (J. Med. Chem.) in the second sentence states that a major problem exists in prodrug design, namely designing the proper derivative. The second paragraph makes the point that some ethyl ester prodrugs are hydrolyzed *in vivo* and some are not. Thus, establishing the lack of predictability in the prodrug area as of 1987. Banker (Modern Pharmaceutics) says on page 451, first paragraph that "preparation of prodrugs is becoming a common practice", implying that it is not routine as of 1996. Banker (Modern Pharmaceutics) says on page 596, third paragraph that "extensive development must be undertaken to find the correct chemical modification". Clearly an invitation to open-ended and potentially inconclusive research.

Wolff (Medicinal Chemistry) in second paragraph in section 10 and the paragraph spanning pages 976-977 indicate the low expectation of success of preparing prodrugs. Since, the prodrug concept is a pharmacokinetic issue, the lack of any standard protocol discussed in the last sentence of this paragraph is particularly relevant. Finally, concerning the amine containing drugs, Shan (J. Pharmaceutical Sci.) indicates in the first paragraph, page 765 that "[a]pplying similar strategies to the preparation of prodrugs of amine-containing drugs is

somewhat more problematic ... because of the stability of the amide bond". Thus indicating that the research program outlined above may be inconclusive when applied to drugs that are amines. This also contradicts the paragraph spanning pages 10 to 11 stating that esters of amines (amides) are prodrugs.

Applicants must recognize that the prodrug attributes of aspirin and hexamine were not recognized for a hundred years after their synthesis. Are Applicants asserting that prodrug synthesis was routine in the nineteenth century?

11. Claim 34 remains rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of diabetes, does not reasonably provide enablement for treatment of "a fructose-1,6-bisphosphatase dependent disease" generally. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Applicants have not demonstrated nor have they alleged there is any correlation between the *in vitro* assay, whose results are described in Table 3, page 133, and clinical efficacy against all fructose-1,6-bisphosphatase dependent diseases. Case law is clear on this point. In an unpredictable art, such as diabetes pharmacology, *in vitro* assays may be used for enablement only if there is a well-established correlation between the assay and clinical efficacy.

Applicants claim 34 and line 9, page 1 implies that all compounds of formula (I) inhibit fructose-1,6-bisphosphatase. To the extent that "a fructose-1,6-bisphosphatase dependent disease" is the condition fructose-1,6-diphosphatase deficiency as Applicants argue, then it is not logical that lack of the enzyme can be treated by compounds that inhibit the enzyme. In fact, it sounds dangerous.

Applicants argue that they are enabled for diabetes. However, the Examiner stated that in the previous office action. Applicants must be enablement for the entire scope of their claims. According to the MPEP §2164.08 "Enablement Commensurate in Scope with the Claims. All questions of enablement are evaluated against the claimed subject matter. The focus of the examination inquiry is whether everything within the scope of the claim is enabled."

12. Claim 36 remains rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of diabetes, does not reasonably provide enablement for treatment of "glycogen storage diseases" generally. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Applicants have not demonstrated nor have they alleged there is any correlation between the *in vitro* assay, whose results are described in Table 3, page 133, and clinical efficacy against any specific disease. Case law is

clear on this point. In an unpredictable art, such as diabetes pharmacology, *in vitro* assays may be used for enablement only if there is a well-established correlation between the assay and clinical efficacy.

Applicants have clarified that these diseases are the enzyme deficiency disorders of seven specific types of glycogenosis as (Cori classification) and as further described in Chen (Principles of Internal Medicine). The Table 347-1 on page 2178 of Chen (Principles of Internal Medicine) teaches that none of these diseases involves fructose-1,6-bisphosphaaste. The only glycogen storage disease involving fructose is type VII, Tarui disease. This disease is caused by a deficiency of the phosphofructokinase enzyme. The Figure 347-1 on page 2177 makes clear that this is a different enzyme than fructose-1,6-bisphosphaaste. Why do Applicants believe that their fructose-1,6-bisphosphaaste inhibitors will be beneficiation for any of these enzyme disorders?

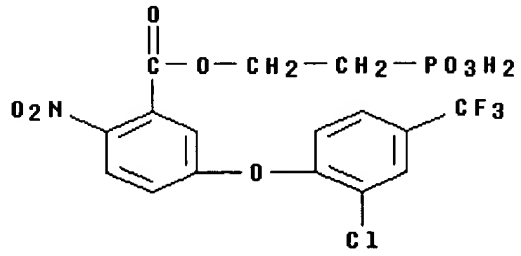
13. Claims 1, 2, 8, 9, 11, 12, 14, 15, 17, 20, and 29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The two provisos in the next to last three lines of claim 1 lack description. Nowhere in the specification is such a

relationship linking the description among radical R^5 and radicals J^2-J^6 described. Such a negative limitation requires description. In *Ex parte Grasselli, et al.* 231 USPQ 393, decided June 30, 1983, the U.S. Patent and Trademark Office, Board of Patent Appeals and Interferences said: "we agree with the examiner's position of record that the negative limitations recited in the present claims, which did not appear in the specification as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112." "It might be added that the express exclusion of certain elements implies the permissible inclusion of all other elements not so expressly excluded. This clearly illustrates that such negative limitations do, in fact, introduce new concepts."

Claim Rejections - 35 USC § 102

14. Claims 1, 2, 8, 9, 11, 12, 14, 15, 17, 20, and 29 remain rejected under 35 U.S.C. 102(b) as being anticipated by Diel ('701). There are two compounds taught in this reference that fit formula (I), one of which is shown below. It has both R^1Y = HO, L = the alkyleneoxycarbonyl group $-CH_2-CH_2-O-C(O)-$, R^5 = disubstituted phenyl, J_2 = nitro, $J^4 = OR^2$, with R^2 = the substituted aryl group phenyl, where the substituents are the halo group chlorine and the perhaloalkyl group CF_3. Line 3, page 5 of the specification discloses that all aryl groups may be substituted. The halo group and the perhaloalkyl group are disclosed as

permissible substituents in line 26 and line 30 of page 5. The compounds are found in the reference in Table I, column 9 and are compounds 1.03 and 1.16.



Applicants' provisos formally overcome this rejection but since those provisos are new matter, the rejection is maintained.

Conclusion

15. Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In

no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

16. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (703) 308-9806. The FAX number for after final amendments is (703) 872-9307. The Examiner is available from 8:30 to 5:30, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Mukund Shah can be reached on (703) 308-4716. Please direct general inquiries or any inquiry relating to the status of this application to the receptionist whose telephone number is (703) 308-1235.

Mukund J. Shah

Mukund Shah
Supervisory Patent Examiner
Art Unit 1624

TCMcK
November 18, 2002